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A Concise Route to Triazolobenzodiazepine Derivatives Via a One-Pot Alkyne-Azide Cycloaddition Reaction

Andrew W. Thomas*

F. Hoffmann-La Roche AG, Pharmaceuticals Division, Discovery Chemistry, Basel, CH 4070, Switzerland

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Abstract—A new and efficient one-pot synthesis of [1,2,3]triazolo[1,5-*a*][1,4] benzodiazepin-6(4*H*)-ones is described starting from readily available anthranilic acids. A small array of the title compounds were assembled via a four-step sequence involving diazotisation, azide addition followed by amide bond formation employing polymer supported carbodiimide and subsequent 1,3-dipolar cycloaddition reaction.

Benzodiazepines have made a tremendous impact on the quality of human life since their introduction, over 40 years ago, for the treatment of central nervous system (CNS) disorders.[1] During this time elegant and practical synthesis of 1,4-benzodiazepines have been developed that allow a diverse array of heterocyclic moieties to be annelated to the benzodiazepine framework.[2] Flumazenil **1** and Estazolam **2**, for example, possess an imidazole and 1,2,4-triazole moiety, respectively, and have found both clinical and commercial success. In addition, G-7453 **3**, which has an annulated tetrazole sub-unit, has recently been reported to have potential utility as a fibrinogen antagonist (Fig. 1).

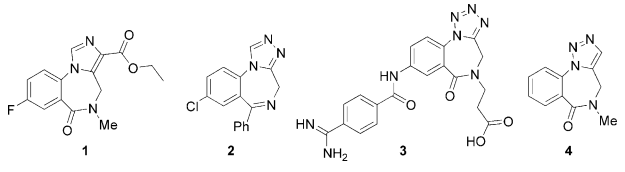

Figure 1. Selected examples of benzodiazepines.

During recent lead evaluation studies within the CNS disease area an efficient synthesis of [1,2,3]triazolo-[1,5-*a*][1,4] benzodiazepin-6(4*H*)-ones **4**, amenable to a parallel chemistry approach was required.

The intramolecular azide-alkyne 1,3-dipolar cycloaddition reaction is a well established method to prepare annulated 1,2,3-triazoles.[3] A route to [1,2,3]triazolo[1,5-*a*][1,4] benzodiazepin-6(4*H*)-ones **4**, from isatoic anhydrides **5**, has recently been reported.[4] However this method was found unsuitable for parallel synthesis, due in part, to the need to carefully extract the intermediate aniline products **6** at alkaline pH. To complement this route it was chosen to optimise for the direct formation of derivative **4** proceeding to the desired targets through an intramolecular azide-alkyne 1,3-dipolar cycloaddition reaction. Additionally, due to the recent popularisation of parallel methodologies in synthetic chemistry it was aimed to design an operationally simplistic protocol amenable to using semi-automated synthesis as well as benefit from the advantages of polymer supported reagents.[5] Herein, we report the realisation of these approaches in the development of a short and reliable synthesis of a small array of tricyclic triazolo-1,4-benzodiazepine derivatives. Two methods explored are outlined in more detail below for comparison.

Chemistry

Isatoic anhydride route (Scheme 1)

In our hands, the treatment of isatoic anhydrides **5** to afford the anilines **6** was best achieved by running the reaction in the presence of catalytic quantities of DMAP according to literature procedures.[6] Following this method, the *ortho*-aminobenzamides **6** were routinely obtained in yields in excess of 85%, along with traces of the urea-acid **8**. In a parallel experiment it was

*Fax: +61-688-6459; e-mail: andrew.thomas@roche.com

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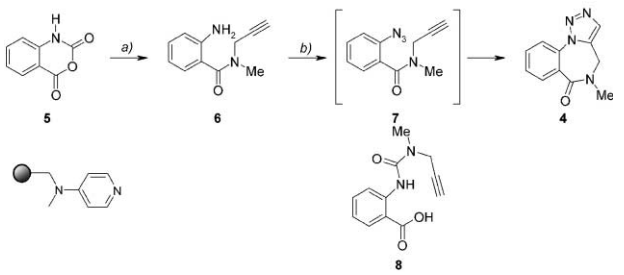
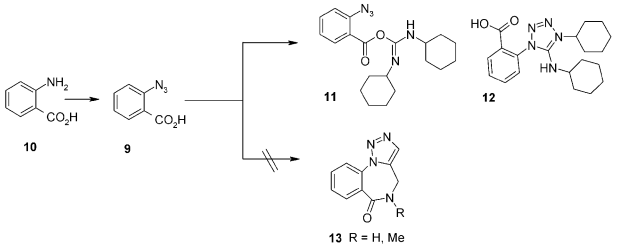


Scheme 1. Route to **4** via isatoic anhydride: Reagents and conditions: (a) PS-DMAP, 0.1 equiv, $MeNHCH_2C{\equiv}CH$, 2.0 equiv, toluene, reflux, 3 h, SiO_2 chromatography, 60%; (b) $NaNO_2$, HCl, NaN_3, toluene, reflux, 2 h, SiO_2 chromatograhphy, 50%.

found that treatment of isatoic anhydride **5** with 2 equiv of *N*-methyl propargylamine and 0.2 equiv of polymer supported DMAP afforded the desired product **6** in 60% yield after chromatography. However substantial quantities of the undesired acid **8** and two additional unidentified impurities were detected by HPLC. Subsequent diazotisation of **6** and in situ azide formation by addition of sodium azide, followed by heating the resulting mixture under reflux in toluene, afforded the tricyclic product **4** in 50% yield, after chromatography, as reported previously.[4] However, this route was not considered satisfactory for parallel synthetic exploitation.

Anthranilic acid route

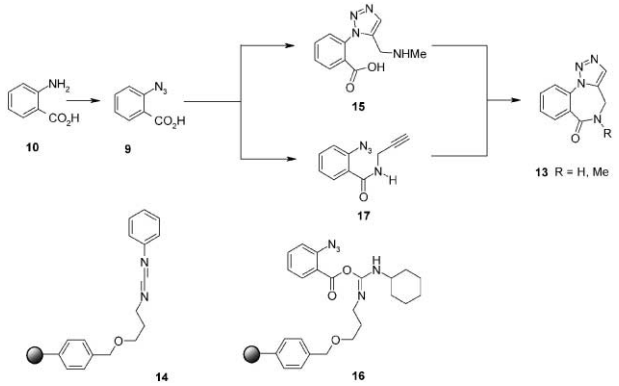
Solution-phase carbodiimides (Scheme 2). Alternative retrosynthetic analysis revealed the intermediate *ortho*-azidobenzoic acid **9**. This can be prepared by diazotisation and an azide displacement reaction of anthranilic acids **10** which proceeded very efficiently following literature precedent.[7] Purification of the products was effected by simply acidifying the reaction mixture resulting in precipitation of the *ortho*-azido benzoic acid products **10**, which were obtained after filtration and drying, in greater than 95% purity and in near quantitative yields, in each case, after removal of the aqueous solution by filtration. Initial attempts to activate the *ortho*-azido acids **9**, towards amide bond formation using conventional solution phase methods (DCCI, EDCI, HOBt, etc.) met with little success and in no case was the desired adduct isolated in pure form. In most instances the activated ester **11** was the main product, isolated in up to 60% yield along with traces of the dipolar cycloaddition product **12**, even after using excess amine and elevated temperatures in attempts to force the reaction to completion.



Scheme 2. Problematic solution-phase route.

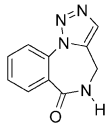
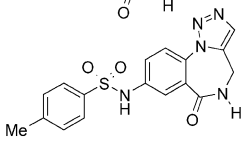
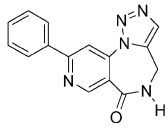
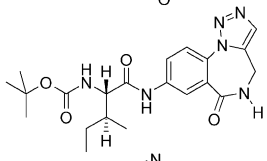
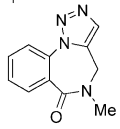
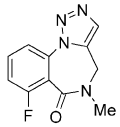
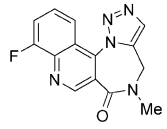
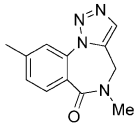
Polymer-supported carbodiimides (Method A: Scheme 3). Surprisingly, employing polymer supported carbodiimides **14** led to a superior reaction.[8] Indeed the desired products **13** (R = Me) could be obtained in high yield and purity by simply filtering the reaction mixture followed by evaporation without the need for chromatographic purification. *This is an example where the use of a polymer supported version of a reagent offers a distinct advantage in both the reaction and in the purification step*. In the event, it was found that the use of 2.0 equiv of polymer supported carbodiimide along with 1.1 equiv of freshly distilled *N*-methyl propargylamine gave the best results. When the reaction was conducted in dichloromethane, the reaction proceeded instantaneously, at room temperature, to form the 1,3-dipolar cycloaddition product **15**, which could be isolated in pure form. The subsequent amide bond formation reaction required reaction times from 30 min to 3 h in order to proceed to completion.[9]

Product isolation required removal of the reaction solution by filtration and evaporation to afford the desired compounds **13** (R = Me) in a pure form. However, when propargylamine was employed a different reaction course took place via **16** and **17**. When the reaction was conducted in the presence of 2.0 equiv of polymer supported carbodiimide along with 1.1 equiv of freshly distilled propargylamine none of the desired product was detected by HPLC. In contrast, it was found that only a small amount of the starting *ortho*-azido acid was recovered. This suggested that the *polymer supported carbodiimide was acting as a sequestering agent for the acid* (in the form of **16**). However, when using excess of the amine (3.5 equiv was optimal) the amide bond formation reaction proceeded smoothly in dichloromethane or toluene at 40 °C to afford **17**, which can be isolated, in quantitative yield, if desired. The subsequent dipolar cycloaddition step [**17**→**13** (R = H)] was sluggish when conducted in dichloromethane requiring reaction times up to 36 h to proceed to completion. In contrast, when carrying out the reaction, in the same pot, in toluene at 70 °C the reaction proceeded to completion within 3 h to afford **13** (R = H). The usual filtration of the reaction mixture, after cooling, followed by evaporation of the filtrate allowed the desired compounds to be isolated in near quantitative yields.



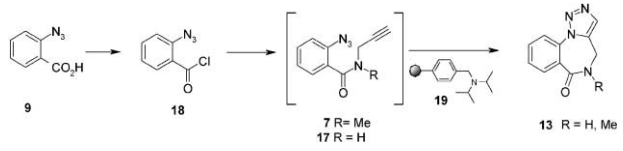
Scheme 3. One-pot supported carbodiimide route.

Table 1. Representative products from 66 examples prepared

Entry	Structure	Yield	MS
1		94%[a] 75%[b]	200.16
2		96%	369.34
3		96%	277.14
4		97%	428.01
5		99%[a] 60%[b]	214.43
6		99%	232.42
7		96%	283.11
8		99%	228.64

[a]Reaction yield following method A.
[b]Reaction yield following method B.

Acid chlorides (Method B: Scheme 4). To complement this route it was further shown that starting from the *ortho*-azido acids **9** it was possible to prepare the desired adducts **13**, via **18** (Scheme 3). The required acid chloride **18** was formed by treatment of **10** with excess thionyl chloride in dichloromethane (in the presence of catalytic dimethylformamide) at ambient temperature for 1 h. Evaporation of the reaction mixture followed by further addition of dichloromethane, 2 equiv of the amine (propargylamine of *N*-methyl propargylamine) and two equivalents of the polymer supported base **19** afforded the reaction products **13** (R = Me, H) in high yield after 15–30 min at room temperature via adducts **7** or **17**, respectively. However, in this case the product purity was somewhat lower (<80%) therefore the route outlined in Scheme 3 was used to prepare a small array of products starting from the appropriate anthranilic acids (Table 1).



Scheme 4. One-pot acid chloride route.

Conclusion

In conclusion, a conceptually simple, short and efficient route to the triclyclic [1,2,3]triazolo[1,5-*a*][1,4] benzodiazepin-6(4*H*)-ones **13**, has been developed employing the use of polymer supported carbodiimide in a key step. The approach has been shown to be suitable for parallel chemical assembly and all products were isolated in high yield and purity without the involvement of chromatographic methods. Application of this methodology to lead generation within CNS projects will be reported elsewhere in due course.

Acknowledgements

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References and Notes

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8. All supported reagents used in this study are commercially available from Argonaut. PS-DMAP (P/N 800288, 1.48 mmol g^{-1}, PS-DCCI (P/N 800371 1.35 mmol g^{-1}) and PS-DIEA (P/N 800279 3.83 mmol g^{-1}). The polymer supported EDCI available from Fluka did not effect the desired tansformation.
9. **Representative procedure for the synthesis of [1,2,3]triazolo[1,5-*a*][1,4] benzodiazepin-6(4*H*)-ones. Method A:** Reactions performed in parallel using the Aronaut Quest 210: To a mixture of the anthranilic acid **10** (1 mmol) was added an aqueous solution HCl (50%, 4 mL) followed by a solution of sodium nitrite (1.05 mmol) in water (1 mL). After 30 min, a solution of sodium acetate (11.1 mmol) in water (2 mL) containing sodium azide (1.1 mmol) was added dropwise and after a further 15 min, the reaction mixture was acidified with HCl (concd 3 drops) whereupon a precipitate formed. The reaction solution was filtered off and the product was dried by purging

with an Argon flow for 15 min. The solid **9** (1 mmol) was then dissolved in dichloromethane (4 mL) and **14** was added (2 mmol). After resin swelling, *N*-methyl propargylamine (1.1 mmol) was added and the reaction agitated for 90 min. Reaction completion was judged by TLC and HPLC. Filtration of the reaction mixture followed by evaporation afforded 5-methyl[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine-6-(4*H*)-one **13** (R = Me) (0.99 mmol, 99%) as a white solid, mp 165–167 °C; ^{1}H NMR ($CDCl_3$) δ 8.1–8.0 (2H, m), 7.7 (1H, s, =NC*H*=C), 7.7–7.6 (3H, m), 4.3 (2H, s, CH_2) and 3.3 (3H, s, NCH_3); ES–MS 214.43 (M^+). Propargylamine (3.5 mmol) can be used in place of *N*-methyl propargylamine and toluene (5 mL) was used as solvent (instead of DCM) and the reaction mixture heated at 70 °C for 3 h. **Method B:** Reactions performed in parallel using the Radleys Carousel: To a mixture of the azido acid **9** (1 mmol) was added thionyl chloride (5 mmol), DMF (1 drop) and the resulting mixture stirred at rt for 1 h. The mixture was then evaporated by attachment of vaccuo to the Argon manifold. To the resulting oil was added dichloromethane (5 mL) followed by propargylamine (2 mmol) and **19** (3 mmol). After 30 min, the reaction mixture was filtered and evaporated to afford [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine-6-(4*H*)-one **13** (R = H) as a white solid (0.75 mmol, 75%), mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 8.2–8.0 (2H, m), 7.8–7.6 (2H, m), 7.7 (1H, s, = NC*H* = C), 4.4 (2H, d, CH_2); ES–MS 200.16 (M^+).